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REVIEW ARTICLE

Therapeutic Strategies and Long-Term Results in Differentiated Thyroid Cancer

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Differentiated thyroid carcinoma (DTC) is usually an indolent tumor associated with a low mortality. However, DTC, particularly papillary thyroid carcinoma, happens to be a multicentric tumor and tends to spread to the regional lymph nodes in the early stage of the disease; some patients with DTC do die from metastatic or recurrent disease. Despite the small number of these patients, therapeutic strategies designed to prevent such outcomes should be pursued. In this review, we attempt to evaluate the impact of different therapeutic strategies on survival and recurrence. Consequently, we conclude that the surgical approach to DIC should be individualized on the basis of the biologic behavior of the tumor, rather than on the extent of cancer involvement in the thyroid and regional lymph nodes. It is mandatory to expand our efforts to identify high-risk patients more accurately, thereby facilitating more rational approaches to treatment. *J. Surg. Oncol. 1998;67:52–59.*

KEY WORDS: thyroidectomy; lymph node dissection; thyroid carcinoma

INTRODUCTION

Papillary and follicular thyroid carcinomas are common forms of thyroid malignancy. They represent more than 85–90% of all thyroid malignancies [1–4] and together are known as differentiated thyroid carcinoma (DTC). Numerous clinicopathologic studies have documented that DTC has an excellent prognosis [1,5,6]. However, DTC, particularly papillary thyroid carcinoma, happens to be a multicentric tumor and tends to spread to the regional lymph nodes in the early stage of the disease [7]; some patients do die from DTC. Several investigators have analyzed various prognostic factors and have found that age, sex, tumor size, histologic type and grade of the tumor, and distant metastases are significant prognostic factors [1–3,8]. Other investigators have introduced scoring systems based on a patient's age, tumor size, tumor grade, and the presence of metastases [9,10]. These prognostic factors and risk analyses have facilitated a more rational approach to the therapy of DTC that avoids overly extensive treatment on the one hand and inadequate therapy on the other.

However, there are considerable controversies concerning not only the extent of thyroidectomy but also the indications for, and the extent of, cervical lymph node dissection [11], although surgical resection is the most effective treatment for DTC. Moreover, there is disagreement about the prophylactic use of radioiodine therapy [12–14]. Although no prospective studies have been performed evaluating the efficacy of surgical treatment and postoperative radioiodine therapy [15,16], the therapeutic approach to DTC should be unified to a more rational approach. We believe that several retrospective studies have given information on the natural history of this disease and have laid out certain guidelines for what may be considered the optimal treatment of DTC. The purpose of this review article is to evaluate the impact of

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several prognostic variables and how surgical treatment and radioiodine therapy influence patient outcome.

PROGNOSTIC FACTORS

Histologic Type and Subtype of Differentiated Thyroid Carcinoma

In differentiated thyroid carcinoma, papillary carcinomas demonstrate a high propensity for regional lymph node metastases but a reduced tendency for distant metastases. In contrast, follicular carcinomas show more of a tendency to metastasize to distant sites [17,18]. However, many studies have revealed no marked differences in patient survival between papillary and follicular carcinomas [19–23]. Recently, several histologic subtypes of DTC have been proposed, along with data suggesting that the identification of the clinicopathologic entity ''poorly differentiated thyroid carcinoma'' is of value in estimating the prognosis of thyroid cancer patients [20,24–27]. Sakamoto et al. [20] have found that the 5-year survival rate for patients with poorly differentiated thyroid carcinoma was 65.0%, or significantly different from that (95.1%) for those with well-differentiated carcinoma. In our previous studies [24,25,28], however, the presence of poorly differentiated thyroid carcinoma appeared to be an important prognostic factor in noncurable disease, but not in curable disease.

Follicular carcinoma demonstrates capsular and/or vascular invasion. Recent prognostic studies have documented that vascular invasion is of greater prognostic importance than capsular invasion in follicular carcinoma [29–32]. Angio-invasive follicular carcinoma is associated with a poor prognosis and a heightened risk of distant metastases, whereas the prognosis of patients with non-angio-invasive follicular carcinoma is almost as good as in those with papillary carcinoma [32]. Davis et al. [33] have reported that the presence of distant metastases, patient age over 50 years, and marked vascular invasion are important prognostic factors for patients with follicular carcinoma. When none or only one of these factors is present, the mortality rates are 1% and 14% at 5 and 20 years, respectively. When two or three factors are present, the mortality rates are 53% and 92%, respectively. Thus, the histologic findings of the tumor alone do not provide sufficient prognostic information for patients with DTC.

Tumor Size and Lymph Node and Distant Metastases

The size of the primary lesion has an important influence on recurrence and survival in papillary thyroid cancer. Nishiyama et al. [34] have found that 13 of 100 consecutive thyroid glands studied at autopsy at the University of Michigan contained small papillary carcinomas. No relationship seems to exist between countries with a high incidence of occult carcinoma of the thyroid found at autopsy and death rates or incidence rates of clinically detectable thyroid cancer [35]. These observations emphasize that very small papillary thyroid carcinomas are extraordinarily common but pose no threat to survival. Woolner et al. [36] have classified papillary carcinoma into occult, intrathyroidal, and extrathyroidal carcinoma. Occult thyroid cancer was defined as 15 mm or less in maximum diameter, with or without local metastases. They observed no deaths from clinically ''occult'' papillary thyroid carcinoma, but found 8 cancer deaths in 348 patients (2.3%) with primary lesions larger than 15 mm [37]. They speculated that occult thyroid cancer may have different biological behavior from ordinary thyroid cancer. However, occult thyroid cancer may not be a separate entity [7,38]. Recently, Noguchi et al. [39] have reported that of 867 patients with small thyroid cancers, defined as a tumor of 10 mm or less, 12 recurrences (1.4%) were observed, and only 2 patients died of thyroid cancer. Thus, death from cancer can occur in patients with small thyroid cancer, although the majority of occult or small thyroid cancers are harmless, as Woolner et al. [36] have speculated.

It has not been established whether the presence of lymph node metastases in DTC implies a poor prognosis. Some investigators have observed no decrease in the survival of patients with node-positive papillary thyroid carcinomas [28–43], whereas others have shown that lymph node metastases influence survival [44,45]. In several studies using multivariate analysis, however, the presence of histologically confirmed lymph node metastases has not been demonstrated to be an unfavorable factor for survival [42,46]. Nevertheless, Harwood et al. [47] have assessed the significance of regional node involvement, matching patients by age, and have found that the recurrence rate is higher in patients with lymph node involvement than in patients without nodal involvement. Thus, nodal metastases increase recurrence rates [5,47,48], but are not widely thought to affect cancer mortality.

There is no doubt that the presence of distant metastases is a dismal prognostic factor in DTC. Nemec et al. [49] have reported the 10- and 15-year survival rates for patients with pulmonary metastases from follicular carcinoma to be 28.9% and 11.4%, respectively. Hoie et al. [50] also have reported that mortality within 1 year of the diagnosis of distant metastases in patients with papillary thyroid cancer exceeded 50%. More recently, however, Smith et al. [51] have reported more favorable results: only a 6.5% mortality rate in their analysis of papillary thyroid carcinoma during 24 years. Harness et al. [52] have reported 20 of 28 patients (71.4%) with pulmonary metastases to be alive 14 years after radioiodine therapy.

Patient-Related Factors and Scoring Systems

Patient-related factors, such as age at diagnosis and gender, have been demonstrated to be related to patient

survival [19,28,43,46]. However, there is considerable disagreement over the relative importance of these factors; the results of multivariate studies are conflicting. In examining the relative importance of risk factors in a disease of low mortality such as DTC, the recurrence-related death rate is of the utmost importance [24,53]. When the characteristics of patients who died following recurrence are compared with those of patients who survived after recurrence, the patient's age has been identified as the most important factor correlated with mortality in several studies [19,24,53].

Cady et al. [9] and Hay et al. [10] have introduced scoring systems for assessing the prognosis of DTC. The AGES system (age, grade, extent and size of tumor) [10] and AMES system (age, metastases to distant site other than lymph nodes, extent and size of tumor) [9] are highly significant in predicting thyroid cancer mortality. Grant et al. [54] have reported that low-risk patients experience less than a 1% risk of thyroid cancer-related death. Undoubtedly, the low-risk patients defined here would not require any adjuvant therapy. In contrast, the observed mortality rate in high-risk patients was significantly higher [54]. For such high-risk patients, more aggressive surgical procedures with postoperative radioiodine therapy and thyroid hormone administration are the treatments of choice. By using these factors and sophisticated multifactorial statistical analysis, their scheme is reasonable and reproducible [10,54]. However, the various scoring systems can be confusing and are too elaborate for easy application in the operating room [9].

DNA Content and Biologic Factors

There has been considerable interest in the possible significance of tumor DNA content in DTC [55]. Hamming et al. [56] have reported that in a study of 113 patients with DTC, DNA content with multiple aberrant stem lines was the only significant prognostic factor for mortality in Cox model multivariate analysis. The prognostic significance of the DNA ploidy pattern has been confirmed in a case-control study from the Mayo Clinic [51]. Although prognostic information has been obtained in this manner in several series, it does not seem to have any prognostic advantage when compared with the AGES or AMES systems. However, recent developments in biochemistry and molecular genetics, involving oncogene and anti-oncogene activation and chromosomal abnormalities, will provide valuable data in clarifying the biologic behavior of DTC [2].

EXTENT OF THYROID CANCER AND CHOICE OF TREATMENT

Thyroid Resection, Intrathyroidal Metastases, and Recurrence

The intrathyroidal dissemination of microscopic foci of cancer is well documented in patients with DTC. Its incidence ranges from 20 to 80%, depending on the extent to which the thyroid is examined [48,57–59]. However, it is not clear whether this represents intrathyroidal metastases or multiple primary tumors arising spontaneously within the gland. There is no definite relationship between the presence of intrathyroidal metastases and tumor size [7,59]. A high percentage of grossly normal, contralateral thyroid lobes contain microscopic tumor foci [57,58,60]. Clark [60] has reported that residual cancer will persist in the remaining tissue in at least 61% of patients if a lobectomy alone is performed.

The degree of thyroid resection for DTC varies from excisional biopsy to total thyroidectomy, while there is a virtual consensus that at least a lobectomy should be performed for a thyroid nodule that may be cancerous [61]. Several investigators have reported that local recurrence rates after total thyroidectomy are lower than those found after less than total thyroidectomy [5,8,54,62–67]. In some of these studies [5,65,67], however, the recurrences included not only intrathyroidal recurrence, but also lymph node recurrence and distant metastases. Local recurrence related to the type of thyroidectomy should be defined as histologically confirmed tumor occurring in the resected thyroid bed, thyroid remnant, or other adjacent tissues of the neck excluding lymph nodes. With agreement of this definition, Grant et al. [54] as well as Hay et al. [8] have reported that local recurrence rates after unilateral lobectomy are significantly higher than after total thyroidectomy (Table I), suggesting that small, multicentric tumors can lead to clinically important, recurrent cancer. In the United States, near-total thyroidectomy is the procedure advocated most often for patients with papillary thyroid cancer. Nevertheless, it is a fact that the development of a recurrent thyroid cancer in the remnant thyroid lobe is considerably less common than the reported incidence of microscopic disease [60,66,68]. Tollefsen et al. [66] have reported a 5.7% local recurrence rate in the contralateral thyroid remnant (17 of 298 patients) (Table I). Seven patients (41%) died of recurrent disease. The authors highlighted the marked discrepancy of clinical local recurrence, only 5.7%, versus what may have been expected if all contralateral microscopic multicentric disease—38% in their study—had actually become manifest. Moreover, Wanebo et al. [69] have reported that there is no difference in survival after total thyroidectomy versus lobectomy. Hay et al. [10] also have reported that survival is not influenced by the extent of thyroid resection in low-risk patients, while only a trend toward improved survival with bilateral thyroid resection, compared with unilateral resection, was observed in high-risk patients (Table I). On the other hand, the complication rate of total thyroidectomy, specifically related to the recurrent laryngeal nerve and the parathyroids, is substantially higher than that of more conservative procedures [61,70–73]. Farrar et al. [73]

TABLE I. Recurrence and Death According to the Extent of Thyroid Resection in Patients With Differential Thyroid Cancer*

Authors and procedures	% of recurrence			% of death		
	LRG		HRG			
Grant et al. [54]						
Unilateral resection (145)	14	$P < 0.001$	–	$P = 0.01$	–	
Bilateral resection (818)	4		–		–	
Tollefsen et al. [66]						
Less than total (298)	5.7 (17)	$P = 0.0292$			–	
Total thyroidectomy (78)	0 (0)				–	
					LRG	HRG
Hay et al. [8,10]						
Ipsilateral lobectomy (39)	20	$P = 0.007$			2 $P = 0.15$	65 $P = 0.07$
Bilateral lobectomy (485)	5				1	35

*[ ], reference number; ( ), number of patients; LRG, low-risk group; HRG, high-risk group; –, not reported.

have reported an incidence of 20.7% hypoparathyroidism and 3.4% recurrent nerve injury in patients undergoing total thyroidectomy. This was reduced to 1.6% hypoparathyroidism and 0.5% recurrent nerve injury in patients treated with a partial thyroidectomy. Therefore, other surgeons strongly endorse total lobectomy with isthmusectomy [69,73].

Lymphadenectomy, Lymph Node Metastases, and Recurrence

With regard to the management of cervical lymph node metastases, there is considerable controversy concerning not only the indication for, but also the extent of cervical lymph node dissection. Although surgical removal of clinically involved cervical lymph nodes is well accepted, it has never been established which type of neck dissection leads to better results in the treatment of patients with clinically involved lymph nodes. Surgical procedures have varied from node plucking (simple local excisions), to modified or classical radical neck dissection. While radical neck dissection is mostly effective, modified neck dissection, which produces less deformity, and spares the spinal accessory nerve, sternocleidomastoid muscle, and jugular vein, is probably equally effective and is currently popular [40]. Mazzaferri and Young [62] have been unable to find a difference in recurrence rates between patients treated by node plucking and those treated by modified or radical neck dissection. McGregor et al. [74] have reported that the recurrence rate after node plucking was significantly higher than after modified neck dissection in patients with extensive nodal involvement, although no difference was found between node plucking and modified or radical neck dissection in patients with minimal nodal involvement (Table II). Hamming et al. [75] have reported no significant difference in survival or recurrence rate between patients treated by node plucking or by modified radical neck dissection, although recurrences occurred less frequently in the explored side of the neck after modified neck dissection (Table II). Therefore, it may be concluded that a modified neck dissection should be performed in patients with clinically involved lymph nodes. On the other hand, McHenry et al. [76] have reported that in 70 patients with nodal disease, there were 10 (16%) recurrences in 63 patients who had been treated with radioiodine, compared with 3 (42%) recurrences in 7 patients not given radioiodine therapy (Table II). This suggests that adjuvant radioiodine therapy after modified neck dissection may be useful in reducing lymph node recurrences in patients with clinically involved lymph nodes.

The necessity for regional lymph node dissection in the absence of clinically involved nodes remains a controversial issue. It is well known that grossly normal lymph nodes removed in prophylactic node dissection reveal microscopic metastases in the majority of papillary thyroid cancers [7,40,77]. The incidence of lymph node metastases in patients without gross evidence of neck lymph node involvement has been reported to range from 21 to 82% [1,40,44,66]. The preoperative detection of nodal involvement has been reported to be accurate only in 20% of the patients [44]. Frazell and Foote [77] have found histologic evidence of lymph node metastases in 84.6% of 182 neck dissection specimens, including 96% of the specimens from patients with clinically positive nodes, and 61.2% of the specimens from patients whose nodes were thought to be clinically uninvolved. Despite the high frequency of microscopic lymph node metastases, only 3–15% of patients with papillary thyroid cancer in whom no prophylactic neck dissection is performed develop nodes at a later time [4,74,78–80]. Black et al. [4] have shown that subsequent nodal recurrence occurred in only 2.9% of 275 patients with intrathyroidal tumors and apparently uninvolved lymph nodes. A discrepancy exists between the presence of microscopic foci of thyroid cancer in the cervical lymph nodes and the observed nodal recurrence rate. Furthermore, postponement of the neck dissection until nodes became palpable or when histologically proven does not seem to affect

TABLE II. Recurrence and Death According to the Extent of Cervical Lymph Node Resection in Patients With Differential Thyroid Cancer*

Author and procedure	% of recurrence		% of death	
McGregor et al. [74]				
Minimal nodal involvement[a]				
Node plucking (26)	35 (9)	NS	8 (2)	NS
Modified neck dissection (7)	29 (2)		14 (1)	
Extensive nodal involvement[b]				
Node plucking (24)	50 (12)	$P = 0.0246$	25 (6)	NS
Modified neck dissection (20)	15 (3)		10 (2)	
Hamming et al. [42]				
Node plucking (32)	6.3 (2)	NS	–	NS
Modified neck dissection (51)	3.9 (2)		–	
McHenry et al. [76]				
With detectable nodal disease				
Lymph node dissection with radioactive iodine (63)	16 (10)	NS	–	NS
Lymph node dissection without radioactive iodine (7)	42 (3)		–	
Without detectable nodal disease				
No lymph node dissection (157)	2 (3)		–	
Attie et al. [1]				
Therapeutic neck dissection (66)	0 (0)		–	
Prophylactic neck dissection (115)	0 (0)	$P = 0.0012$	–	
No neck dissection performed (97)	7 (7)		–	

*[ ], reference number; ( ), number of patients; –, not reported..
[a]Less than five positive nodes.
[b]Five or more positive nodes.

prognosis [81]. Therefore, some surgeons have recommended a ''wait and see'' policy for patients with no clinical cervical lymphadenopathy or proven metastatic thyroid cancer within the lymph nodes [41,69,82].

However, it is a fact that the regional lymph nodes are the most common site of recurrence, which occurs alone or concomitant with local or systemic recurrence [5,48,69,76]. McHenry et al. [76] as well as Rosen and Maitland [83] have recommended that node sampling should be incorporated into the operative strategy for thyroid cancer to permit intelligent selection of patients for modified neck dissection. However, one problem with this approach is that the site of the metastatic nodal involvement does not correlate well with the location of the tumor within the thyroid gland [84]. The cervicomediastinal lymph nodes are classified into four compartments: (1) cervicocentral compartment; (2) right cervicolateral compartment; (3) left cervicolateral compartment; and (4) mediastinal compartment [43]. Coburn and Wanebo [43] have reported equal number of patients with cervicocentral and cervicolateral node metastases (37%). However, Noguchi et al. [7] have reported that only 20% of patients with DTC had isolated cervicocentral node metastases, while 67% had both cervicocentral and cervicolateral lymph node metastases. The rates of cervicomediastinal node metastases have been reported to range between 6% and 12% [11]. As a general rule, lymph node metastases of the cervicocentral compartment are of greater significance and these lymph nodes should be completely excised in all patients with operable thyroid cancer. On the other hand, metastases to the cervicolateral compartment rarely affect life expectancy, but the dissection of the cervicolateral compartment is expected to reduce the lymph node recurrence rate in patients with thyroid cancer [74]. This lymph node dissection can be performed with little additional morbidity [85]. For these reasons, some surgeons have advocated and performed prophylactic neck dissection [1,42,43,44, 85]. Attie et al. [1] have reported that the incidence of recurrent thyroid cancer in the regional lymph nodes has been decreased by performing prophylactic lymph node dissection (Table II). To base a surgical strategy solely on survival data ignores the problems of locoregional recurrence, which include the increased risk of reoperation, the patient's mental anguish, and the considerable time and expense of repeated evaluation and reoperation [54].

Radioiodine Treatment and Thyroid Hormone Replacement

Radioiodine is effective in the treatment of both papillary and follicular thyroid carcinoma. The benefit of this therapy is apparent only in those who undergo total thyroidectomy [86]. There is little doubt that patients with distant metastases that concentrate radioiodine should receive radioiodine therapy. However, there is disagreement about the use of radioiodine therapy in patients who do not initially have distant metastases. Some investigators [5,67,87] have treated large numbers of patients with near-total thyroidectomy and radioiodine,

TABLE III. Recurrence and Death According to Radioiodine Therapy in Patients With Differentiated Thyroid Cancer*

Author and procedure	% of recurrence		% of death	
Samaan et al. [67]				
Ablative radioiodine (180)	7 (13)	$P < 0.009$	–	NS
No ablative radioiodine (302)	23 (69)		–	
Mazzaferri et al. [5]				
Ablative radioiodine (350)	16	$P < 0.001$	3	$P = 0.03$
No ablative radioiodine (802)	38		6	
McHenry et al. [13][a]				
Ablative radioiodine				
Group 1 (21)	14 (3)		5 (1)	
Thyroid hormone alone		$P < 0.0001$		$P = 0.0061$
Group 2 (44)	1.6 (1)		0 (0)	
Group 3 (169)	0 (0)		0 (0)	
Varma et al. [14]				
Ages (0–39 years)				
Ablative radioiodine (179)	–		3.4 (6)	NS
Surgery alone (18)	–		5.6 (1)	
Ages (40 or >40 years)				
Ablative radioiodine (84)	–		25 (21)	$P < 0.005$
Surgery alone (32)	–		59.4 (19)	

*[ ], reference number; ( ), number of patients; –, not reported.
[a]Group 1 included residual thyroid in six, micrometastases in lymph nodes in seven, and lung metastases in eight; Group 2 had evidence of extrathyroidal tumor spread or metastatic disease at operation; Group 3 had no evidence of extrathyroidal tumor spread or metastatic disease at operation.

while others [12] have argued that few patients with papillary thyroid carcinoma should be treated with radioiodine therapy. Samaan et al. [67] as well as Mazzaferri and Jhiang [5] have reported that radioiodine therapy prolonged disease-free survival in low-risk patients in whom recurrences were reduced by half; the death rate was also significantly lower (Table III). Therefore, Mazzaferri and Jhiang [5] have concluded that near-total thyroidectomy followed by radioiodine therapy plus thyroid hormone administration confers a distinct outcome advantage for tumors 15 mm or more that are not initially metastatic to distant sites. However, McHenry et al. [13] have found no recurrences in patients with DTC without local tumor extension or regional or distant metastases who were treated with postoperative thyroid hormone therapy, and they have recommended that radioactive therapy be omitted for these patients (Table III). Varma et al. [14] also have reported no significant difference in death rates between patients under 40 years of age treated with radioiodine therapy versus those treated with surgery alone, while the former group had a significantly lower death rate than the latter in patients 40 years of age and older (Table III).

It has been advocated that total thyroidectomy following radioactive therapy is the standard treatment for all patients with follicular carcinoma [60,88]. Samaan et al. [65] have found that follicular and mixed tumors show a significantly lower recurrence rate when ablative iodine is administered, while the disease-free interval and survival are not significantly different. However, other authors point to the lack of clear evidence that such surgical treatment following radioiodine therapy is needed or justified [82]. Total thyroidectomy followed by radioiodine therapy should be indicated for the high-risk patients with follicular carcinoma. As mentioned above, it may be indicated for patients aged over 50 years with marked angio-invasive follicular carcinoma [89]. In addition, there is doubt about the effectiveness of thyroid hormones in reducing the tumor mass and in preventing subsequent recurrences of the cancer. However, all agree that thyroid hormone should be given postoperatively in sufficient doses to suppress endogenous thyrotropin.

CONCLUSIONS

1. DTC has a relatively indolent biologic behavior. However, it happens to be a multicentric tumor and tends to spread to the regional lymph nodes in the early stages of disease; some patients do die from this cancer.

2. Surgical resection is the most effective treatment for DTC, but the extent of resection needed is controversial. Extensive or aggressive surgical resection decreases locoregional recurrences but does not appear to affect cancer-related mortality. The complication rate after aggressive surgical procedures is substantially higher than after more conservative procedures.

3. To base a surgical strategy solely on survival data ignores the problems of locoregion recurrences. Locoregional control and the morbidity of treatment are equally important considerations in determining the optimal treatment of DTC.

4. Total thyroidectomy followed by radioiodine

therapy is effective in prolonging overall and disease-free survival.

Therefore, therapeutic strategies should be individualized on the basis of the biologic behavior of the DTC, rather than on the extent of cancer involvement in the thyroid and regional lymph nodes. It is mandatory to expand our efforts to identify high-risk patients more accurately, thereby facilitating more rational approaches to the treatment of thyroid cancer. In the meantime, the treatment strategy of thyroid cancer must be made on the basis of available but imperfect data.

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